from equation: $v^{calc} = [CD\cdot1]\ v_c/[1]_0$, while in turn the concentrations of the complex, [CD·1], are calculated from formula 5a in the appendix. The best v_c values are those which minimize the error square function $U = \sum_i (v_i - v_i^{calcd})^2$ and are found through repeated parabolic interpolation.

Acknowledgment. We thank Dr. F. Reniero for his skillful participation, E. Castiglione for technical assistance, and the Ministry of Public Education (Italy) for financial support.

Appendix

Derivation of Equation 2. The kinetic expressions for the formation of 2 and 3 from free (1) and complexed (CD·1) substrates are

$$v_i = k_i^f[1] + k_i[CD\cdot1] \qquad (i = 2, 3) \qquad (1a)$$

and may be rearranged to

$$v_i = k_i^f[1]_0 + \Delta k_i[CD\cdot1] \qquad (2a)$$

where $\Delta k_i = k_i - k_i^f$. Under the assumption that the ratio between v_2 and v_3 does not change significantly during the greatest part of the reaction period (which has been verified in the case of the reduction of **1b**), the ratio v_2/v_3 is also the product ratio [2]/[3].

Derivation of Equation 3. For the generic complexation equilibrium

$$1 + CD \rightleftharpoons CD\cdot1 \qquad (3a)$$

with binding constant K_b, the chemical shift of any substrate signal is given by

$$v = v_0[1]/[1]_0 + v_c[CD\cdot1]/[1]_0 \qquad (4a)$$

which reduces to the second term in the second member when the shifts are referred to the measure taken in water, v_0. When the smallest $[CD]_0$ is $\geq 10[1]_0$, the constant reduces to

$$K_b = [CD\cdot1]/\{([1]_0 - [CD\cdot1])[CD]_0\} \qquad (5a)$$

Substitution in (4a) gives (3).

Registry No. **1a**, 930-68-7; **1b**, 1193-18-6; **1c**, 78-59-1; **2a**, 108-93-0; *cis*-**2b**, 5454-79-5; *trans*-**2b**, 7443-55-2; *cis*-**2c**, 933-48-2; *trans*-**2c**, 767-54-4; **3a**, 822-67-3; **3b**, 21378-21-2; **3c**, 470-99-5; heptakis(2,6-*O*-methyl)-β-CD, 51166-71-3; α-CD, 10016-20-3; β-CD, 7585-39-9; heptakis(6-*N*-methyl)-β-CD, 55137-65-0; heptakis(6-*N*-methyl-*N*-acetyl)-β-CD, 99965-65-8.

Resolution and Absolute Configuration of K-Region Trans Dihydrodiols from Polycyclic Aromatic Hydrocarbons

S. K. Balani, P. J. van Bladeren, N. Shirai, and D. M. Jerina*

Laboratory of Bioorganic Chemistry, NIADDK, National Institutes of Health, Bethesda, Maryland 20892

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K-region trans dihydrodiols of benzo[*c*]phenanthrene, chrysene, pyrene, and dibenz[*c*,*h*]acridine have been resolved as their diastereomeric diesters with (−)-(menthyloxy)acetic acid, and their absolute configurations have been assigned by the application of circular dichroism and exciton chirality methods. For these as well as the K-region trans dihydrodiol derivatives from five other hydrocarbons, a consistent pattern of physical properties has emerged. The *R*,*R* diastereomers are less retained on silica gel HPLC columns when eluted with ether–cyclohexane mixtures and show negative values of $[\alpha]_D$ in tetrahydrofuran, the degree of magnetic nonequivalence between H_A and H_B in the $-OCH_AH_BCO_2-$ portion of the diesters (100 MHz, C_6D_6) is generally much higher for the *S*,*S* enantiomers of the dihydrodiols, and the free *R*,*R* dihydrodiols have positive values of $[\alpha]_D$ in tetrahydrofuran provided their hydroxyl groups do not have a marked preference for the pseudodiaxial conformation.

Cytochrome P450 catalyzed formation of K-region arene oxides represents a common pathway in the metabolism of polycyclic aromatic hydrocarbons in mammals. With liver microsomes from 3-methylcholanthrene treated rats, K-region trans dihydrodiols formed by the subsequent action of microsomal epoxide hydrolase on these arene oxides often represent major metabolites: benzo[*e*]pyrene (34%), benz[*a*]anthracene (42%), phenanthrene (69%), and benzo[*c*]phenanthrene (89%).[1] The absolute configuration of these K-region dihydrodiols is of considerable interest from the standpoint of the stereospecificity of the cytochromes P450 which form their precursor arene oxides,[2] of the regiospecificity of epoxide hydrolase in their conversion to dihydrodiols,[3] and of the mechanism of their conjugation with glucuronic acid.[4] To date, only phenanthrene 9,10-dihydrodiol has been assigned absolute configuration directly by chemical correlation with tartaric acid.[5] Subsequently, benzo[*a*]pyrene 4,5-dihydrodiol (after reduction of the chromophore) was assigned[6] through application of an exciton chirality experiment.[7] Assignments of the phenanthrene 9,10-dihydrodiol (a bridged biphenyl chromophore whose conformationally dependent CD spectrum is related to its helicity)[8-10] and the benzo[*a*]-

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Table I. Physical Properties of Resolved K-Region Trans Dihydrodiols and Their Diesters with (-)-(Menthyloxy)acetic Acid

parent hydrocarbon	$[\alpha]_D$ (THF), deg, of the diesters with (-)-(menthyloxy)acetic acid		NMR (100 MHz, C_6D_6) of diesters: $-OCH_ACH_BCO_2-$ splitting (mult)	NMR (100 MHz, C_6D_6) of diesters: K-region signals (ppm) ($J_{K\text{-region}}$, Hz)	$[\alpha]_D$ (THF) dihydrodiols (**1c–9c**), deg	ref
phenanthrene (1)	less polar (9*R*,10*R*)	−238 (**1a**)	3.62 (s)	6.37	+162	this study[a]
	more polar (9*S*,10*S*)	+161 (**1b**)	3.52, 3.76 (d)	6.35	−172	
benz[*a*]anthracene (2)	less polar (5*R*,6*R*)	−260 (**2a**)	3.64 (s)	6.54, 6.69 (4.6)	+198	this study[b]
	more polar (5*S*,6*S*)	+92 (**2b**)	3.52, 3.76 (d)	6.42, 6.58 (4.6)	−205	
benzo[*c*]phenanthrene (3)	less polar (5*R*,6*R*)	−326 (**3a**)	3.66 (s), 3.74 (s)	6.36, 6.50 (6.0)	+407	this study
	more polar (5*S*,6*S*)	+109 (**3b**)	3.54, 3.80 (d); 3.64, 3.86 (d)	6.36, 6.48 (6.0)	−393	
chrysene (4)	less polar (5*R*,6*R*)	−498 (**4a**)	3.42 (s); 3.58 (s)	6.53, 7.38 (2.9)	−460	this study[c]
	more polar (5*S*,6*S*)	+259 (**4b**)	3.44, 3.58 (d); 3.50, 3.70 (d)	6.52, 7.37 (2.9)	+469	
pyrene (5)	less polar (4*R*,5*R*)	−382 (**5a**)	3.60 (s)	6.79	+17	this study[d]
	more polar (4*S*,5*S*)	+211 (**5b**)	3.48, 3.76 (d)	6.76	−14	
benzo[*a*]pyrene (6)	less polar (4*R*,5*R*)	−299 (**6a**)	3.60 (s); 3.64 (s)	6.86, 6.96 (~4)	+39	6
	more polar (4*S*,5*S*)	+147 (**6b**)	3.48, 3.76 (d); 3.52, 3.80 (d)	6.86, 6.97 (~4)		
6-fluorobenzo[*a*]pyrene (7)	less polar (4*R*,5*R*)	(**7a**)	3.50 (s); 3.61 (s)		−44	14
	more polar (4*S*,5*S*)	(**7b**)	3.37, 3.63 (d); 3.52, 3.70 (d)			
dibenz[*c*,*h*]acridine (8)	less polar (5*R*,6*R*)	−268 (**8a**)	3.67 (s); 3.68 (s)	6.49, 6.57 (4.4)	+157	this study
	more polar (5*S*,6*S*)	+120 (**8b**)	3.56, 3.81 (d); 3.58, 3.81 (d)	6.47, 6.55 (4.4)	−167	
7,12-dimethylbenz[*a*]-anthracene (9)	less polar (5*R*,6*R*)	−273 (**9a**)	3.54 (s); 3.63, 3.73 (d)	6.50, 7.06 (3.7)	−218	this study[e]
	more polar (5*S*,6*S*)	+126 (**9b**)	3.64 (s); 3.43, 3.61 (d)	6.31, 6.85 (3.7)	+200	

[a] See ref 5 for assignment. This sign of rotation of the dihydrodiol (ϵ_{269} 17 000, THF) does not change between THF and chloroform. [b] The present rotations represent an improvement over the earlier assignment study (ref 11). [c] The dihydrodiol has ϵ_{266} 71 500 in THF. [d] The dihydrodiol has ϵ_{258} 46 400 in THF. As has been shown previously (ref 6) for benzo[*a*]pyrene 4,5-dihydrodiol (**6c**), the $[\alpha]_D$ for pyrene 4,5-dihydrodiol (**5c**) changes sign when measured in THF vs. methanol (+17° vs. −144°, respectively). The basis for these solvent-dependent sign changes are presently unknown. [e] See text and ref 13 for assignment where the (+)-(5*S*,6*S*)-dihydrodiol has $[\alpha]_D$ +257° in methanol. A value of $[\alpha]_D$ +243° in methanol was obtained in the present study. The dihydrodiol has ϵ_{271} 53 300 in THF.

pyrene 4,5-dihydrodiol have provided anchor structures to which other dihydrodiols have been correlated. For example, an exciton chirality experiment has been used to correlate the configuration of benz[*a*]anthracene 5,6-dihydrodiol,[11] after reduction to a biphenyl chromophore, with that of phenanthrene 9,10-dihydrodiol. Subsequently several 7-alkyl- and 7-halo-substituted benz[*a*]anthracene 5,6-dihydrodiols,[12] as well as 7,12-dimethylbenz[*a*]-anthracene 5,6-dihydrodiol,[13] were assigned by comparison of their CD spectra with the parent compound. Similarly, comparison of CD spectra of 6-halobenzo[*a*]pyrene 4,5-dihydrodiols with the unsubstituted dihydrodiol has allowed their assignments.[14,15] Configurational assignments of the glutathione conjugates of K-region arene oxides in which the hydroxyl and *S*-glutathionyl substituents are pseudodiaxial have been similarly related.[16] Recent studies of the K-region *cis*- and *trans*-9,10-dihydrodiols of 4,5-dimethyl- as well as 3,4,5,6-tetramethylphenanthrene have been particularly interesting.[4,17] Due to steric interference between the methyl groups, rotation about the biphenyl axis is severly hindered such that individual conformational isomers can be isolated. In the cis case, these conformers are enantiomers whose structures can be assigned from their CD spectra based on the helicity of the biphenyl chromophore. In the trans case, stable pairs of conformers are isolable from each enantiomer and their structure similarly assigned.

Boyd and co-workers have noted that the degree of magnetic nonequivalence between H_A and H_B in the $-OCH_AH_BCO_2-$ entity of (-)-(menthyloxy)acetyl esters of trans bromohydrins on saturated benzo rings of polycyclic aromatic hydrocarbons is related to the chirality of the oxygen-bearing ring carbon.[18] This same relationship has been found to hold for the bis((-)-(menthyloxy)acetates) of related benzo ring trans dihydro- and tetrahydrodiols[19,20] but has never been applied to K-region trans dihydrodiols. The data in Table I summarize our present knowledge of such K-region derivatives. All of these dihydrodiols have been resolved as their diastereomeric diesters with (-)-(menthyloxy)acetic acid. Data for phenanthrene (**1**), benz[*a*]anthracene (**2**), benzo[*a*]pyrene (**6**), and 6-fluorobenzo[*a*]pyrene (**7**) are partially or entirely from prior studies (see notes to Table I). The basis for assignment of absolute configuration to the K-region trans dihydrodiols of benzo[*c*]phenanthrene (**3**), chrysene (**4**), pyrene (**5**), and dibenz[*c*,*h*]acridine (**8**) was obtained in the present study, which also includes a cross-correlation of the present methods with a previous assignment[13] of the K-region dihydrodiol of 7,12-dimethylbenz[*a*]anthracene (**9**).

Results and Discussion

Chromatographic Resolution of Dihydrodiols. All of the trans K-region dihydrodiols described in the present study have been resolved by HPLC as their diastereomeric diesters with (-)-(menthyloxy)acetic acid (Table I) on Du Pont Zorbax SIL columns. Values of α (separation factor) for the separation ranged from 1.15 to 1.23 with values of

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(12) See for selected examples at the K-regions of 7-methyl (Yang, S. K.; Fu, P. P. *Chem.-Biol. Interact.* **1984**, *49*, 71–88), 7-bromo (Fu, P. P.; Yang, S. K. *Carcinogenesis* **1983**, *4*, 979–984), 7-chloro (Fu, P. P.; Von Tungeln, L. S.; Chou, M. W. *Mol. Pharmacol.* **1985**, *28*, 62–71), 7-fluoro (Chiu, P.; Fu, P. P.; Yang, S. K. *Cancer Res.* **1984**, *44*, 562–570), and 12-methyl (Fu, P. P.; Chou, M. W.; Yang, S. K. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 940–946) benz[*a*]anthracene as well as references therein. Of particular interest to the present discussion is the negative rotation (THF) for the (5*R*,6*R*)-dihydrodiol of 7-fluorobenz[*a*]anthracene which has pseudodiaxial hydroxyl groups. Also of interest are the reported analytical separations of enantiomeric dihydrodiols on chiral HPLC stationary phases (Yang, S. K.; Weems, H. B.; Mushtaq, M. *J. Chromatogr.* **1984**, *316*, 569–584).
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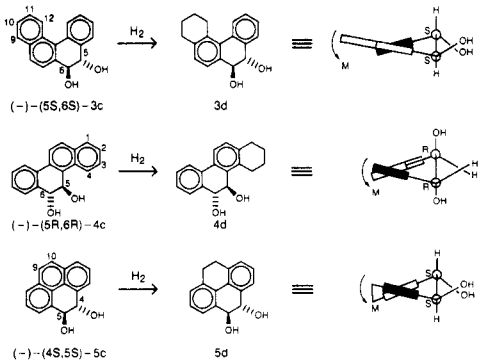

Figure 1. Reduction of K-region dihydrodiols to biphenyl chromophores. For the reduced benzo[*c*]phenanthrene (**3d**) and chrysene (**4d**) derivatives, the open bars represent the cyclohexylphenyl portions of the molecules.

k' from 1.1 to 3.5 with 6–10% ether in cyclohexane as the eluting solvent. Although the diesters from chrysene (**4a**, **4b**) failed to separate under these conditions, 0.3% dioxane in dichloromethane (α = 1.20 with *k'* = 1.3 and 1.6) proved satisfactory. Notably the early eluting (less polar) diester of each pair had a negative value of $[\alpha]_D$ while the late eluting (more polar) diastereomer had a positive value of $[\alpha]_D$. As will be established, the less polar diastereomers (negative $[\alpha]_D$) all have *R,R* absolute configuration. The sign of rotation for the free dihydrodiols also showed a trend that appears to be conformationally dependent: the *R,R* enantiomers have positive values of $[\alpha]_D$ provided that they do not show a marked preference for the conformation with pseudodiaxial hydroxyl groups (i.e., **1c–3c**, **5c**, **6c**, **8c**). The *R,R* enantiomers with pseudodiaxial hydroxyl groups (i.e., **4c**, **7c**, **9c**) have negative values of $[\alpha]_D$. In general, K-region trans dihydrodiols tend to show a marked preference for the conformation in which the hydroxyl groups are pseudodiequatorial in the absence of unusual structural factors.[8,21] Thus, the chrysene 5,6-dihydrodiol (**4c**) forms part of a hindered bay region, the 7,12-dimethylbenz[*a*]anthracene 5,6-dihydrodiol (**9c**) suffers steric interaction between the 7-methyl and 6-hydroxyl groups, and the 6-fluorobenzo[*a*]pyrene 4,5-dihydrodiol (**7c**) has an adverse electrostatic interaction between the 6-fluoro and 5-hydroxyl groups causing these three dihydrodiols to prefer the pseudodiaxial conformation.

Assignment of Absolute Configuration. The chiroptical properties of bridged biphenyls have been extensively studied[3d,4,8–10,16,17] with the result that right-handed (P, plus) helicity looking down the biphenyl axis is associated with a strong, positive CD band in the region of 225–235 nm. Conversely, a negative band in this region is associated with left-handed (M, minus) helicity. The position of the CD band is dependent on the nature of substituents which can preturb the UV chromophore, and the intensity of the CD band is linearly related[4] to conformational preferences of the molecule in question as this determines the magnitude of the helicity.

The strategy utilized to assign the *trans*-5,6-dihydrodiols of benzo[*c*]phenanthrene (**3**) and chrysene (**4**) is illustrated in Figure 1. The terminal benzo ring of the naphthyl portion of each dihydrodiol ((−)-**3c** and (−)-**4c**) was reduced (PtO_2, 3 atm H_2, 3 days) to a cyclohexyl-fused phenanthrene 9,10-dihydrodiol. Conformation of the diol groups was established to be predominantly pseudodiequatorial in **3d** ($J_{5,6}$ = 10.3 Hz) and pseudodiaxial in **4d** ($J_{5,6}$ = 2.9 Hz) based on their NMR spectra. Both phenanthrene

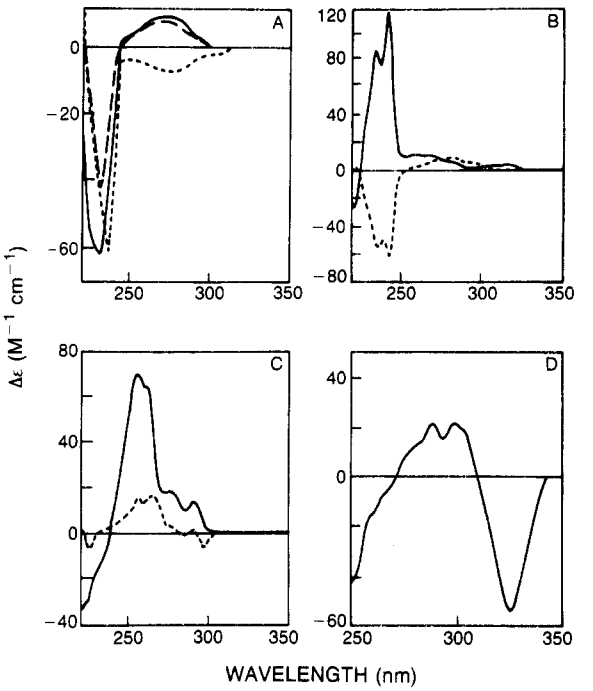

Figure 2. Circular dichroism spectra determined in freshly distilled THF except as noted. (A) Spectrum of phenanthrene (−)-(9*S*,10*S*)-dihydrodiol (solid line, **1c**) compared to the hexahydrodiols derived from the benzo[*c*]phenanthrene (−)-(5*S*,6*S*)-dihydrodiol (dashed line, **3d**) and chrysene (−)-(5*R*,6*R*)-dihydrodiol (dotted line, **4d**). See Figure 1 for structures. (B) Spectra of the tetrahydrodiol (dotted line, **5d**) derived from pyrene (−)-(4*S*,5*S*)-dihydrodiol (**5c**, Figure 1) and the di-MTPA ester of **5d** (solid line). (C) Spectra of the (−)-(4*S*,5*S*)-dihydrodiol of pyrene (Figure 1, **5c**) and its di-MTPA ester (solid line). (D) Spectrum (55% THF in water) of the bis(*p*-(dimethylamino)-benzoate) of the (+)-(5*R*,6*R*)-dihydrodiol of dibenz[*c*,*h*]acridine (**8c**). The concentration of the CD sample was based on $\epsilon_{365\ nm}$ 15 800 for the free dihydrodiol in THF.

trans-9,10-dihydrodiol (**1c**)[4,8] and the reduced benzo[*c*]-phenanthrene 5,6-dihydrodiol (**3d**) prefer the conformation in which the hydroxyl groups are pseudoequatorial in organic solvents. The negative CD band ($\Delta\epsilon_{233\ nm}$ −62) for (−)-phenanthrene (9*S*,10*S*)-dihydrodiol (**1c**) is paralleled by a negative CD band ($\Delta\epsilon_{233\ nm}$ −42) for **3d** when derived from (−)-**3c** (Figure 2A). Thus the biphenyl chromophores in both molecules have M-helicity (Figure 1) which requires 5*S*,6*S* absolute configuration for (−)-**3c**. In the case of chrysene 5,6-dihydrodiol (**4c**) and the resulting hexahydrodiol (**4d**), both prefer the conformation in which the hydroxyl groups are pseudoaxial due to steric hindrance in the bay region. The strong negative CD band ($\Delta\epsilon_{238\ nm}$ −60) of **4d** derived from (−)-**4c** (Figure 2A) also requires M-helicity. Thus the (−)-chrysene 5,6-dihydrodiol must have 5*R*,6*R* absolute configuration (Figure 1).

The closely related (+)-5,6-dihydrodiol of 7,12-dimethylbenz[*a*]anthracene has been reduced to its 5,6,8,9,10,11-hexahydro derivative. The exciton chirality experiment used to assign absolute configuration of the bis((dimethylamino)benzoate) ester of this hexahydrodiol is not readily interpretable;[22] however, the observed strong,

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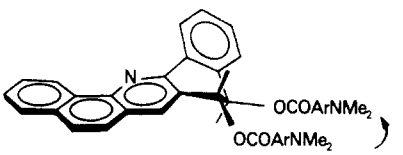
(22) The CD spectrum of the bis(*p*-(dimethylamino)benzoate) of the hexahydrodiol was reported to have a positive maximum at 317 nm, pass through zero ~292 nm, and have a negative maximum ~277 nm. Although these maxima have been attributed[13] to an exciton interaction between the benzoates, the CD bands are sufficiently far from the usual wavelengths (typically $\Delta\epsilon$ = 0 in the region 315 nm with extrema around 300 and 330 nm) that this interpretation is questionable. As the benzoates are essentially locked in the pseudodiaxial conformation of the 7-methyl group, little electric dipole interaction between them could be expected in any event.

positive CD band[13] at 238 nm due to the skew biphenyl chromophore in the free diaxial diol provides the information necessary for unambiguous configurational assignment as *S,S*.[9,10] The observation of nearly identical CD bands in the region of 230 nm for **3d** and **4d** of opposite configuration is noteworthy in that the chiral centers bearing the hydroxyl groups clearly contribute little to the observed spectra. Such does not appear to be the case for the regioisomeric glutathione adducts derived from the dissymmetric K-region arene oxides of benz[*a*]anthracene and benzo[*a*]pyrene where positional isomers with the same absolute configuration have CD spectra with much different shapes.[16]

A similar approach has been taken in assignment of absolute configuration to the *trans*-4,5-dihydrodiols of pyrene (**5c**). In this case, reduction of the remaining K-region 9,10-double bond (Figure 1) results in the desired biphenyl chromophore. Although symmetry precludes the direct use of proton NMR (cf. ref 8, 10) to deduce the conformation of (−)-**5c** and the derived tetrahydrodiol (**5d**), it is reasonable to assume that **5d** prefers the conformation in aprotic organic solvents in which its hydroxyl groups are pseudodiequatorial (Figure 1). The negative CD band ($\Delta\epsilon_{243\,nm}$ −61; Figure 2B) for **5d** derived from (−)-**5c** requires M-helicity and thus 4*S*,5*S* absolute configuration in both molecules. Since the pyrene assignment is entirely dependent upon the presumed pseudo-diequatorial conformation for the hydroxyl groups in tetrahydrodiol **5d**, additional evidence for this conformation was sought. In a recent study[23] we had noted that formation of diester with (−)-α-methoxy(trifluoromethyl)phenylacetic acid (MTPA) was a particularly effective way by which the conformer population of the benzo[*c*]phenanthrene 5,6-dihydrodiol (**3c**) could be shifted ($J_{5,6}$ = 10.3 Hz for the free dihydrodiol and 3.5 Hz for the di-MTPA ester in $CDCl_3$). Thus **5d** was converted into its di-MTPA ester, and the CD spectrum of the ester was determined (Figure 2B). The observation of an even stronger but now positive CD band ($\Delta\epsilon_{243\,nm}$ +118) requires P-helicity, a result which can only be compatible with preferred pseudodiaxial substituents in the diester and with a pseudodiequatorial conformation for the hydroxyl groups in **5d**. The decreased magnitude of the CD band for the tetrahydrodiol **5d** relative to its diester is indicative[10] that **5d** has only a partial preference for the pseudodiequatorial conformation.

The present assignment of absolute configuration to the pyrene 4,5-dihydrodiols is strengthened by comparison with the studies of Armstrong and co-workers[16] on the glutathione-S-transferase (isozyme C) catalyzed trans addition of glutathione to the symmetric substrate pyrene 4,5-oxide. The predominant adduct (axial substituents) has a strong positive CD transition at 265 nm and was assigned 4*S*,5*S* absolute configuration. The strongest CD bands (THF) for the (−)-(4*S*,5*S*)-dihydrodiol are in this same region ($\Delta\epsilon_{254-265\,nm}$ +18) but are of low intensity (Figure 2C). As the bis-MTPA ester, however, a very strong, positive band ($\Delta\epsilon_{253-263\,nm}$ +71), consistent with that of the 4*S*,5*S* glutathione conjugate, was observed. Since both the free dihydrodiol and its bis-MTPA ester have positive bands, the CD determinations suggest that the dihydrodiol may exist in THF with a significant amount of the conformation in which the hydroxyl groups are pseudodiaxial. Of the several glutathione adducts studied,[16] the *S,S* enantiomers (pseudodiaxial in water) all had CD spectra whose predominant bands were positive.

As the K-region 5,6-dihydrodiol of dibenz[*c,h*]acridine (**8**) is a major metabolite of the hydrocarbon,[24] assignment of absolute configuration to this trans dihydrodiol was also of interest. Assignment has been achieved in part by an exciton chirality experiment[7] and in part by analogy to other compounds in this study. The (+)-dihydrodiol **8c** derived from the less polar (early eluting) bis(menthyloxyacetate) **8a** was converted into a diester with *p*-(dimethylamino)benzoyl chloride. Although this diester proved to be insufficiently stable to allow accumulation of enough material for an NMR spectrum, its formation was certain based on its mass spectrum and a strong UV band at 320 nm with a shoulder at 295 nm. The position and high intensity (~4-fold stronger than UV bands of the free dihydrodiol[20]) of this band suggests a strong electric transition dipole interaction between the benzoate chromophores as necessitated for an exciton chirality experiment. That such an interaction was present was evidenced by the CD spectrum of the derivative (Figure 2D); a very strong negative band at 325 nm ($\Delta\epsilon$ −54.6), zero at 311 nm, and a positive band at 299 nm ($\Delta\epsilon$ +20.7). Although the sign and λ_{max} of the extrema of the Cotton effects are as expected for *R,R* absolute configuration (negative longer wavelength band), the 299-nm band is only half as intense as the 325-nm band. Since CD effects of the starting



dihydrodiol ((+)- or (−)-**8c**) are rather weak in this region ($\Delta\epsilon_{284,294\,nm}$ ~6), we assume the presence of a negative contribution to the CD curve resulting from interaction between the dihydrodiol chromophore and the (dimethylamino)benzoates (295-nm shoulder in the UV spectrum) in the short wavelength region. Nevertheless, the high intensity of the 325-nm band along with analogies to other *R,R* dihydrodiols in Table I provide sufficient justification to assign 5*R*,6*R* absolute configuration to (+)-**8c**.

Correlation of Physical Properties. The diastereomeric diesters with (−)-(menthyloxy)acetic acid show a nearly complete parallel between three physical properties and their absolute configuration: the *R,R* enantiomers (i) elute first from silica gel HPLC columns, (ii) have large, negative values of $[\alpha]_D$ in THF, and (iii) generally show magnetic equivalence between the pairs of diastereotopic hydrogens H_A and H_B in the $-OCH_AH_BCO_2-$ group in their (menthyloxy)acetic acid esters, whereas the reverse is true for the *S,S* enantiomers. All NMR spectra were run at 100 MHz in C_6D_6, and values of J_{gem} were 16 ± 0.5 Hz when nonequivalence was observed at this field strength. Depending on the degree of nonequivalence between H_A and H_B in a given ester and on the difference in chemical shift between the two $-OCH_2CO_2-$ groups in a given diastereomer, the four hydrogens can appear as a single signal or as many as eight lines. The simplest and clearest examples (Table I) are the pairs of diastereomers from phenanthrene (**1**), benz[*a*]anthracene (**2**), and pyrene (**5**) where the *R,R* diastereomers show a single line and the *S,S* diastereomers show an apparent quartet due to overlap of the pairs of doublets from the two esters (Figure 3). More complex examples (Table I) consist of the diastereomers from **3**, **4** and **6-8** where the *R,R* isomers show two lines and the *S,S* isomers show from six (overlap of two pairs,

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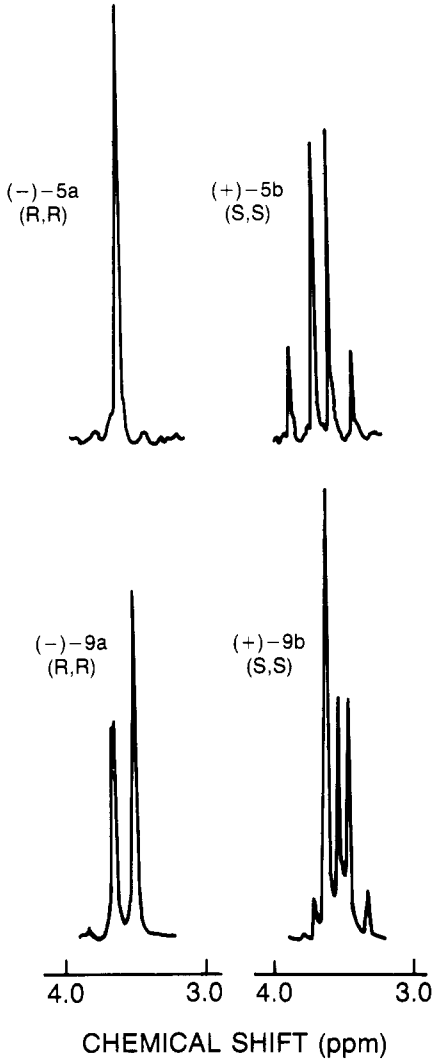

Figure 3. NMR signals (100 MHz, C_6D_6) for the $-OCH_2CO_2-$ portion of the di-menthyloxyacetate diastereomers from pyrene 4,5-dihydrodiols (**5c**) and 7,12-dimethylbenz[*a*]anthracene 5,6-dihydrodiols (**9c**).

8b) to eight lines. In all of the above examples, the pairs of signals for H_A and H_B are completely or very nearly equivalent in the *R,R* isomers and are clearly nonequivalent (much more complex pattern) for the *S,S* isomers at 100 MHz. The only case where assignment by NMR alone would be difficult is that of 7,12-dimethylbenz[*a*]-anthracene (**9**) where a small amount of splitting is observable for one of the $-CH_2-$ signals in the *R,R* isomer (**9a**) and no splitting is observable for one of the $-CH_2-$ signals in the *S,S* isomer (**9b**) in contract to the general trend (Figure 3). This problem was not encountered with the diastereomers from chrysene (**4**) in which the substituents are even more axial ($J_{5,6}$ = 2.9 Hz for **4a,b** compared to $J_{5,6}$ = 3.7 Hz for **9a,b**). The basis of the magnetic nonequivalence between H_A and H_B in any of these esters is presently unknown.

Conclusion

In summary, several criteria are described which may be utilized to assign absolute configuration to K-region trans dihydrodiols of polycyclic aromatic hydrocarbons. Examples of dihydrodiols that are largely pseudodiaxial and pseudodiequatorial, as well as a dihydrodiol derived from an azapolycyclic hydrocarbon have been considered. Although the chiroptical methods are perhaps the most reliable methods of assignment, significant correlations exist between absolute configuration and retention times on HPLC as well as rotations for the diastereomeric esters with (−)-(menthyloxy)acetic acid. The degree of nonequivalence between H_A and H_B in these esters provides a useful but perhaps less reliable correlation. Provided that there is not a substantial contribution of the pseudodiaxial conformation to the overall conformer population, *R,R* dihydrodiols at K-regions have positive values of $[\alpha]_D$ in THF. This is contrasted to results on 14 benzo ring, trans dihydrodiols for which the *R,R* enantiomers have negative values of $[\alpha]_D$ in THF regardless of preferred conformation.[25]

Experimental Section

NMR spectra were recorded at 100 or 300 MHz with tetramethylsilane as an internal standard. Chemical ionization mass spectra were with NH_3 gas. Optical rotations and CD spectra (10 mm cylindrical cell) were measured in freshly distilled THF except as noted.

Racemic K-Region Trans Dihydrodiols. The *trans*-5,6-dihydrodiol **8c** of dibenz[*c,h*]acridine which was obtained by hydrolysis of the 5,6-oxide as described[20] and the dihydrodiols **1c–5c** and **9c** were prepared by reduction of the corresponding quinones with borohydride in alcohol as first reported by Dey and Neumeyer.[26] In a typical experiment, a suspension of 400 mg of quinone and 1 g of potassium borohydride in 100 mL of 2-propanol was vigorously stirred in an open Erlenmeyer flask at room temperature overnight. After standard workup, the dihydrodiols were purified by flash chromatography on silica gel, initial elution with chloroform to remove quinone followed by elution with 10% methanol in chloroform to isolate the dihydrodiols. Yields were generally in excess of 80%. Only in the cases of 7,12-dimethylbenz[*a*]anthracene[27] and chrysene (~10%) was any of the cis dihydrodiol isomer detected. The *trans*-4,5-dihydrodiol of pyrene (**5c**) proved to be unstable and had to be stored at ~0 °C to prevent autoxidation back to quinone.

Phenanthrene 9,10-quinone was obtained from Aldrich Chemical Co. K-region quinones of benzo[*c*]phenanthrene (**3**) and chrysene (**4**) were prepared by chromic acid oxidation of the parent hydrocarbons.[28,29] In the case of benz[*a*]anthracene (**2**) and pyrene (**5**), the corresponding K-region, cis dihydrodiols (obtained by oxidation of the hydrocarbons with osmium tetraoxide) were oxidized to quinones with active manganese dioxide (0.5 g of cis dihydrodiol and 2 g of MnO_2 in 150 mL of dichloromethane, stirred overnight). In the case of the *cis*-5,6-dihydrodiol of 7,12-dimethylbenz[*a*]anthracene, oxidation with manganese dioxide resulted in exclusive cleavage to the dialdehyde. Separate experiments established that the desired quinone was stable to the oxidation conditions. Furthermore, attempted oxidation of the cis dihydrodiol to the 5,6-quinone with either Me_2SO–acetic anhydride[30] or SO_3–pyridine[31] as previously described failed to provide acceptable yields of the desired quinone; in each case, the dialdehyde was formed as the predominant product. However, pyridinium chlorochromate[32,33] reproducibly effected the desired oxidation. A mixture of cis dihydrodiol (0.2 g), sodium acetate (0.1 g), and the oxidant (0.4 g) in dichloromethane (5 mL) was stirred for 2 h at room temperature during which time two additional portions (0.1 g) of oxidant were added. Workup consisted of filtration through a pad of Florisil. NMR of the crude product indicated complete conversion to a mixture of the desired quinone

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along with dialdehyde (methyl signals at δ 2.93 and 3.04 and at δ 2.34 and 3.01, respectively) in a ratio of 65:35. Pure quinone, identical with that previously described,[30,31] was readily obtained by crystallization from acetone at 4 °C.

Resolution of Trans Dihydrodiols. All dihydrodiols (Table I) were resolved as their diesters with (-)-(menthyloxy)acetic acid. Typically, a solution of trans dihydrodiol (0.4 g) and (-)-(menthyloxy)acetyl chloride (1.0 g) in pyridine (1.5 mL) was stored at 4 °C for 1 day. Reaction was terminated by addition of water, and the products were extracted into ether. After standard workup, the esters were purified by passage through a dry silica column eluted with 10–15% ether in cyclohexane. Data for the separation of the diastereomers by HPLC and their properties are given in the text and table. The diastereomeric diesters (100 mg) were hydrolyzed (150 mg of sodium methoxide, 4 mL of 50% methanol in THF, 10–20 min under N_2). Pure samples of dihydrodiols for rotations and CD measurements were obtained by HPLC on Du Pont Zorbax SIL columns eluted with 3–5% methanol and 15% ethyl acetate in hexane.

Reduction of Trans Dihydrodiols to Biphenyl Chromophores. The (-) enantiomers of **3c**, **4c**, and **5c** (0.2 mmol in 30 mL of THF) were agitated under 1 atm of H_2 for 3 days in the presence of added platinum oxide (0.6 mmol). After filtration to remove catalyst and concentration, the reaction products were purified by preparative TLC on silica gel plates eluted 2–3 times with 4% methanol in chloroform. In each case, the higher R_f band corresponded to reduced material. Typically, ~20% of the starting dihydrodiol was reduced. Cited UV spectra which follow were recorded in THF.

(a) *trans*-5,6-Dihydroxy-5,6,9,10,11,12-hexahydrobenzo[*c*]phenanthrene (3d) obtained by reduction of (-)-**3c** was purified by HPLC on a Du Pont Zorbax SIL column (9.45 × 250 mm) eluted with 1.2% ethyl acetate and 12% dioxane in cyclohexane; k' = 3.3 and 4.6 for **3d** and **3c**, respectively. For **3d**: MS (CI, NH_3) 284 (M^+ + 18), 266 (M^+ + 18 - H_2O); NMR (300 MHz, $CDCl_3$) $H_{5/6}$ δ 4.48, 4.56 with $J_{5,6}$ = 10.3 Hz. The UV spectrum showed a broad λ_{max} at 269 nm with ε 13 300 characteristic of a biphenyl chromophore.

(b) *trans*-5,6-Dihydroxy-1,2,3,4,5,6-hexahydrochrysene (4d) obtained by reduction of (-)-**4c** was purified on the above column eluted with 1% methanol and 15% ethyl acetate in cyclohexane; k' = 8.0 and 10.3 for **4d** and **4c**, respectively. For **4d**: MS (EI) 266 (M^+), 248 (M^+ - H_2O); NMR (300 MHz, $CDCl_3$) $H_{5/6}$ δ 4.75 and 5.04 with $J_{5,6}$ = 2.9 Hz. The UV spectrum showed a broad λ_{max} at 277 nm with ε 18 000 characteristic of a biphenyl chromophore.

(c) *trans*-4,5-Dihydroxy-4,5,9,10-tetrahydropyrene (5d) obtained by reduction of (-)-**5c** was purified on the above column eluted with 5% methanol and 15% ethyl acetate in cyclohexane; k' = 1.5 and 1.8 for **5d** and **5c**, respectively. Although the fraction thought to be **5d** appeared homogeneous by HPLC on the SIL column, NMR spectroscopy indicated the presence of a second diol in about twice the amount as **5d**. Further HPLC on a Du Pont Zorbax ODS column (9.45 × 250 mm) eluted with 15% water in methanol allowed separation of **5d** (k' = 0.76) from the major reduction product (k' = 1.26). For **5d**: MS (EI) 238 (M^+), 220 (M^+ - H_2O); NMR (300 MHz, $CDCl_3$) $H_{4/5}$ δ 4.73 and $H_{9/10}$ 2.85 as singlets. The UV spectrum showed a broad λ_{max} at 283 nm (ε 14 500) with shoulders at 274 and 294 nm. The presence of such shoulders has been observed previously in doubly bridged biphenyls.[6,34] The major reduction product proved to be *trans*-4,5-dihydroxy-1,2,3,3a,4,5-hexahydropyrene with unknown stereochemistry(s) at C_{3a}: MS (EI) 240 (M^+), 222 (M^+ - H_2O); NMR (300 MHz, $CDCl_3$) δ H_4 3.50 (t) and H_5 4.80 (d) with $J_{4,5}$ = 9.3 Hz and $J_{3a,4}$ = 10.5 Hz. The UV spectrum showed a sharp λ_{max} at 232 nm with a broad λ_{max} at 287 nm which is only 7% as intense.

Bis(*p*-(dimethylamino)benzoate) of *trans*-5,6-Dihydroxy-5,6-dihydrodibenz[*c*,*h*]acridine ((+)-8c). *p*-(Dimethylamino)benzoyl chloride (16 mg), *p*-(dimethylamino)pyridine (3 mg), and the (+)-dihydrodiol (2 mg) in pyridine (100 μL) were stored at 75 °C for 15 h. Water was added and the product was extracted into chloroform. After standard workup, a THF solution of the crude product was purified by HPLC on a Du Pont Zorbax ODS column (0.62 × 25 cm); initially 50% THF in H_2O with a linear gradient programmed over 6 min to 55% THF in water at a flow rate of 1.5 mL/min. The bis-ester was collected at a retention time of 14.4 min. Instability of the bis-ester precluded obtaining an NMR spectrum. MS (CI-NM_3) m/z 608 (M^+ + 1). Its UV spectrum (55% THF in H_2O) was dominated by a broad band at 320 nm with a shoulder at 295 nm. The starting dihydrodiol has a λ_{max} at 295 nm (ε 23 000) and a weaker absorption at 365 nm (ε 15 800). The 365-nm absorption is also present in the bis-ester but only one-fifth as intense as the exciton interaction band at 320 nm.

Registry No. **1a**, 78306-72-6; **1b**, 78246-26-1; (+)-**1c**, 64440-29-5; (-)-**1c**, 23190-41-2; (±)-**1c**, 25061-61-4; **2**, 56-55-3; **2** (5,6-dione), 18508-00-4; (±)-**2** (cis-diol), 78307-15-0; **2a**, 101313-14-8; **2b**, 101313-15-9; (+)-**2c**, 64440-28-4; (-)-**2c**, 64440-27-3; (±)-**2c**, 67315-17-7; **3**, 195-19-7; **3** (5,6-dione), 734-41-8; **3a**, 99922-15-3; **3b**, 101313-16-0; (+)-**3c**, 100017-13-8; (-)-**3c**, 101313-22-8; (±)-**3c**, 101313-28-4; **3d**, 101226-69-1; **4**, 218-01-9; **4** (5,6-dione), 2051-10-7; (±)-**4** (cis-diol), 101313-29-5; **4a**, 101226-63-5; **4b**, 101313-17-1; (+)-**4c**, 77123-20-7; (-)-**4c**, 101313-23-9; (±)-**4c**, 67175-78-4; **4d**, 101226-70-4; **5**, 129-00-0; **5** (4,5-dione), 6217-22-7; **5** (cis-diol), 51689-88-4; **5a**, 101226-64-6; **5b**, 101313-18-2; (+)-**5c**, 101313-24-0; (-)-**5c**, 101313-25-1; (±)-**5c**, 101226-68-0; **5d**, 101226-71-5; **6a**, 78088-16-1; **6b**, 78031-10-4; (±)-**6c**, 50700-50-0; **7a**, 101226-65-7; **7b**, 101313-19-3; (±)-**7c**, 101313-30-8; (±)-**8** (5,6-oxide), 93716-20-2; **8a**, 101226-66-8; **8b**, 101313-20-6; (+)-**8c**, 101313-26-2; (+)-**8c** (4-(dimethylamino)benzoate), 101226-72-6; (-)-**8c**, 101313-27-3; (±)-**8c**, 93716-21-3; **9**, 57-97-6; **9** (5,6-dione), 18508-00-4; **9** (dialdehyde), 963-87-1; (±)-**9** (cis-diol), 64265-59-4; **9a**, 101226-67-9; **9b**, 101313-21-7; (+)-**9c**, 92693-64-6; (-)-**9c**, 92693-65-7; (±)-**9c**, 75262-88-3; 9,10-phenanthrenedione, 84-11-7.

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Lanthanides in Organic Synthesis. 3. A General Procedure for Five- and Six-Membered Ring Annulation

Gary A. Molander* and Jeffrey B. Etter

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

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An improved method for cyclization of 2-(ω-iodoalkyl)cycloalkanones utilizing samarium diiodide (SmI_2) has been developed. Both five- and six-membered rings can be constructed in excellent yields for the first time by such a process. The reaction takes place under very mild conditions, allowing toleration of a number of functional groups under the reaction conditions. Stereochemical aspects of the reaction have been delineated. The reaction has been found to be highly stereoselective when cyclization takes place onto cyclopentanone substrates and when 2-substituted-2-(ω-haloalkyl)cycloalkanone precursors are utilized.

Ring annulation represents an exceedingly important transformation in organic synthesis. As such, numerous methods have been developed to carry out this type of process.[1] Among the more attractive approaches due to

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